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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/832,233	04/10/2001	John A. Kink	OPHD-06331	8942

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EXAMINER	
SHAREH, SHAHNAM J	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 12/31/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/832,233	KINK ET AL.	
	Examiner	Art Unit	
	Shahnam Sharareh	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 10, 2003 has been entered.

Claims 1-14 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treating Necrotizing Enterocolitis (NEC) with hen or avian anti-TNF antibodies as set forth in the instant examples 1, does not reasonably provide enablement for all anti-TNF antibodies encompassed by the recited anti-TNF antibodies encompassed in claims 1, 9. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

In particular, the specifications fail to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to In *re Wands*, 858 F.2d 731, 8 USPQ2d 1400, 1404, Fed. Cir. 1988. The

court sets forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing E*x part Forman*, 230 USPQ 546 (BDApls 1986) at 547 the court recited eighth factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence of absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art

7) the predictability of the art, and

8) the breadth of the same.

The requirement under 112, 1st paragraph demands that the patent specification to enable those skilled in the art to make and use the full scope of the claimed invention without undue experimentation. The instant specification only describes a given antibody that possesses a desired anti-TNF characteristic in treating NEC. Specification fails to enable one of ordinary skill in the art the entire class of anti-TNF antibodies that can be employed for treating NEC. In fact, there is no direction as to the specific domains, molecular weight, or sedimentation coefficients, etc.. of antibodies hereby claimed to treat NEC. Accordingly, the teachings in the specification appear to provide no more than an invitation to experiment.

Specifically, the state of the prior art concerning methods of treating NEC is unpredictable. There are not clear understanding of how NEC may be treated.

Moreover. There are at least two types of TNFs, alpha and beta. There is no predictability in the art as to which type of TNF potentiates NEC.

The instant examples do not describe the in vivo correlation among the entire class of anti-TNF polyclonals and treatment of NEC. Rather they are limited to theoretical assumptions in uniformity of response among all claimed anti-TNF polyclonal antibodies. The antibodies disclosed do not represent the entire class of anti-TNF antibodies. Thus, there is lack of adequate guidance to practice the claimed scope and the ordinary skill in the art would have needed to perform undue experimentations to identify the which anti-TNF antibodies are effective in treating NEC.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 1-5, 9-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eibl et al US Patent 5,833,984 ("Eibl II") in view of Muguruma et al (Prenat Neonat Med 1998;3:571-579), Eibl I (Acta Pediat 83,666-668, 1994).

Eibl discloses methods of using anti TNF- antibodies to reduce the inflammatory response caused by gram-negative bacterimia (col2, lines 7-10). Eibl further teaches the correlation between levels of TNF and the pathogenesis of neonatal NEC (see col 1, lines 60-66). Eibl further teaches various modes of administration of antibodies to a patient (col 6, lines 5-20). Eibl fails to specifically use anti-TNF antibodies in treating NEC.

The role of TNF in the development of neonate NEC has been well established in the art. Accordingly, Wolf, Eibl I and Muguruma are merely used to set forth general knowledge in the art about TNF and NEC.

Wolf, for example, describes the general knowledge about the affects of oral IgA-IgG preparations in inhibiting TNF release thereby preventing the development of pathological changes associated with NEC in low-birth-weight infants (p. 667, 4th para).

Eibl I sets forth successful use of IgA-IgG in treating or preventing NEC among human infants (see abstract, discussion).

Muguruma also teaches the role of TNF in the pathogenesis of NEC and ultimately the development of said condition specifically in low-birth-weight neonates (see abstract, entire document). Muguruma indicates the important role of pro-inflammatory agents such as TNF (page 575, 2nd, 3rd para-page 576, 2nd para.). Muguruma et al, however, fails to specifically teach the use of antibodies directed to PAF as a means of decreasing PAF activity among susceptible patients.

Eibl, Maguruma, and Wolf teach methods of treating conditions that are caused by over expression of pro-inflammatory factors, therefore, their teachings are viewed as being in the same field of endeavor.

The role of TNF as a pro-inflammatory mediator in development of necrotic enterocolitis has been well established in the art as shown by Maguruma and Wolf. Accordingly, even tough Eibl II does not explicitly disclose the use of anti-TNF antibodies in treating NEC in neonates, it would have been obvious to one of ordinary skill in the art at the time of invention to employ such products for treatment of NEC, because as suggested by Muguruma and Eibl I and Wolf.

The ordinary skill in the art would have had a reasonable expectation of success in employing anti-TNF for treating NEC, because it is well established that TNF potentiates the progress of NEC and thus, reducing the effects of TNF activity among human infants would improve or alleviate the pathological changes that would lead to NEC. Examiner states that any degree of relief from NEC would read on the scope of

the instant claims, and the ordinary skill in the art would have had a reasonable expectation of success in at least observing some symptomatic relief when administering the anti-TNF taught by Eibl.

Response to Arguments

Applicant's arguments filed October 10, 2003 have been fully considered but they are not persuasive.

Applicant first argues that the art is not adequate for rendering the instant claims obvious. Specifiacally, Applicant appears to be arguing that just because TNF is a pro-inflammatory mediator, it is not enough to motivate one of ordinary skill in the art to use an antibody directed to TNF for a particular mode of treatment, i.e. treatment of NEC.

In response, Examiner states the prior art not only teaches the use of anti-TNF antibodies for treatment of an inflammatory condition, but also makes clear that TNF plays an integral role in the progress of NEC (see all the secondary references). Therefore, one of ordinary skill in the art would have been motivated to use such antibodies to treat any other disease potentiated by TNF as the inflammatory mediator. NEC is one of such diseases.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a

reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, all elements of the instant claims are met and the combination of cited references are based on the level of ordinary skill in the art. Therefore, the conclusion of obviousness is not based on hindsight, rather, prima facia obviousness.

Conclusion

No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shahnam Sharareh whose telephone number is 703-306-5400. The examiner can normally be reached on 8:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, PhD can be reached on 703-308-1877. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1123.

RUSSELL TRAVERS
PRIMARY EXAMINER

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